UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/467,397	06/06/95	FRANK B	HYZ-041

EXAMINER
WEISS, J

18N2/0528

LAPPIN & KUSMER
200 STATE STREET
BOSTON MA 02109

ART UNIT	PAPER NUMBER
1805	8

DATE MAILED: 05/28/96

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/467,397	Applicant(s) Frank et al.
	Examiner Bonnie Weiss	Group Art Unit 1805

☒ Responsive to communication(s) filed on *Jun 6, 1995* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-206* is/are pending in the application.

Of the above, claim(s) *52-206* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-51* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-206* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part II DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-51, drawn to oligonucleotides that are complementary to the HBV genome, a kit comprising the same, and a pharmaceutical composition comprising the same, classified in Class 536, subclass 22.1.

Group II. Claims 52-131, drawn to methods of use, classified in Class 514, subclass 44.

Group III. Claims 132-156, drawn to oligonucleotides complementary to noncontiguous regions of the HBV genome and a pharmaceutical composition comprising the same, classified in Class 536, subclass 22.1.

Group IV. Claims 157-26, drawn to a kit for inhibiting HBV replication comprising and methods of use of the "noncontiguous" oligos, classified in Class 514, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P.

§ 806.05(h)). In the instant case, oligonucleotides that are complementary to the HBV genome could also be used as hybridization probes or reagents for detection of HBV in cells as well as a putative therapeutic agent.

3. Inventions III and IV are also related as product and process of use and are considered to be distinct inventions for the same reason.

4. Inventions I and III are disclosed as different combinations which are not connected in design, operation or effect. These combinations are independent if it can be shown that (1) they are not disclosed as capable of use together, (2) they have different modes of operation, (3) they have different functions, or (4) they have different effects. (MPEP 806.04, MPEP 808.01). In the instant case the combinations have potentially different modes of operation since the first set of oligonucleotides could potentially anneal to both DNA and RNA species, whereas the second set of oligonucleotides would be targeted to predicted regions of secondary structure in the HBV RNA.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

6. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, and the search required for Group I is not required for

Group III, etc., restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Anne-Louise Kerner on May 3, 1996, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-51. Affirmation of this election must be made by applicant in responding to this Office action. Claims 52-206 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 17, 19 and 40-44 are rejected under 35 U.S.C. § 102(b) as being anticipated by either Wu et al. (IDS, B4) or Wu

et al. (WO 93/04701-A1). Claim 45, 48 and 50 are also rejected under 35 U.S.C. § 102(b) as being anticipated by Wu et al. (PCT WO 93/04701-A1).

Claim 1 is drawn to an oligonucleotide complementary to a portion of the HBV RNA having a nucleotide sequence selected from the group consisting of SEQ ID NOs 1-31 and 42-48. Claims 17 and 19 recite more narrowly oligos having SEQ ID NOs 16 and 18, respectively. The oligos defined by SEQ ID NOs 16 and 18 are designated as oligo HBV101 and HBV71 in Table 1 on page 16 of the specification, which also defines the complementary regions of the HBV genome as extending from positions 1903 to 1922, and 1910 to 1921, respectively, both of which are part of the "poly A" region as diagrammed in Figure 1.

The other rejected claims recite an oligo of claim 1 which comprises at least one deoxyribonucleotide (Claim 44) or one ribonucleotide (Claim 45), or is modified (Claim 40), more narrowly defined as comprising at least one internucleotide linkage selected from the group listed in Claim 41, more specifically recited as an oligo comprising at least one phosphorothioate internucleotide linkage (Claims 42 and 43). Claims 48 and 50 are drawn to a kit and a pharmaceutical composition comprising at least one nucleotide of Claim 1.

Wu et al. (B4) utilize a 21-mer oligodeoxynucleotide complementary to a portion the ayw subtype of HBV corresponding to nucleotides 1903-1923 of the viral genome. The oligo was

synthesized with phosphorothioate linkages (see Materials and Methods, lines 15-20). Wu et al. (the PCT) teach the same oligonucleotide on page 12, line 1, which is also defined in the PCT as SEQ ID NO 1. This oligo is coextensive with those defined by SEQ ID NOs 16 and 18. On page 2, Wu et al. state that the oligo may be DNA or RNA, and on pages 9-10, Wu et al. discuss pharmaceutical compositions containing the oligo for the treatment of HBV infection. In the absence of unexpected results demonstrating that a shorter version of the oligo taught by Wu et al. would be beneficial, the oligos of the instant invention are anticipated by the oligo of Wu et al., and thus the references anticipate Claims 1, 17, 19, 40-44, and also 45, 48 and 50, respectively.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. Claims 18 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over either Wu et al. (IDS, B4) or Wu et al. (WO 93/04701-A1) in view of Ono et al. (Nucleic Acids Res., 1983, 11(6): 1747-1757).

The claims are drawn to the oligonucleotide of claim 1 having SEQ ID NOs 17 and 19, respectively. SEQ ID NOs 17 and 19 correspond to oligos HBV94 and HBV93 and are complementary to positions 1903-1929 and 1910-1929, respectively. Each of these oligos overlap the complementary region of SEQ ID NO 16, but also overlap the PolyA region described in Figure 1.

Both references by Wu et al. teach an oligonucleotide that encompasses the oligo of SEQ ID NO 16 as discussed above. Wu et al. do not teach the specific oligonucleotide sequences as defined by SEQ ID NOs 17 and 19.

Ono et al. teach the entire sequence of the HBV genome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligo taught by Wu et al. inhibited HBV replication, to use the sequence taught by Ono et al. to design other oligonucleotides

that were complementary to the PolyA region for the purpose of inhibiting HBV replication.

13. Claims 46 and 47 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (WO 93/04701-A1) in view of Uhlmann et al. (Chemical Rev., 1990, 90(4): 544-584).

Claim 46 is drawn to the oligo of Claim 44 (which contains at least one deoxyribonucleotide as described above), further comprising at least one ribonucleotide. Claim 47 is drawn to the oligonucleotide of Claim 45 (which contains at least one ribonucleotide as described above), further comprising at least one 2'-O-methyl nucleotide.

As stated above, Wu et al. teaches HBV oligos that may be either DNA or RNA. Wu et al. does not specifically teach an oligo containing both DNA and RNA, nor an oligo containing a 2'-O-methyl nucleotide.

Uhlmann et al. discuss chimeric RNA/DNA oligonucleotides on page 573, column 1, lines 9-12, as a means of creating site-specific cleavages in a target molecule using RNase H.

Uhlmann et al., on page 558, column 1, section 2, discuss 2'-O-methyl oligoribonucleotide derivatives and the use of such a modification to increase the stability of oligoribonucleotides.

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the oligos taught by Wu et al. with the modifications taught by Uhlmann et al. for the purpose of

generating site-specific cleavages in HBV RNA and increasing the stability of the HBV-directed oligonucleotides.

14. Claims 1-9, 33-35 and 37-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Oh et al. (Korean J. Biochem., 1993, 25: 115-120) in view of Ono et al. (Nucleic Acids Res., 1983, 11(6): 1747-1757).

The claims are drawn to an oligonucleotide complementary to a portion of the HBV RNA having a nucleotide sequence selected from the group consisting of SEQ ID NOs 1-31 and 42-48 (Claim 1), more narrowly recited in Claims 2-9 as an oligonucleotide having SEQ ID NOs 1-8, respectively, or in Claims 33-35 and 37-39 as having SEQ ID NOs 42-44 or 46-48, respectively. These oligos are described in Table 1 and Figure 1 as being complementary to the last 50 nucleotides of the X gene coding region, and the initiation region of the polymerase coding region, respectively.

Oh et al. teach the use of antisense oligonucleotides complementary to the S, X, and P genes of HBV (the abstract). The oligos used by Oh et al. are not identical to the oligos of the instant application.

Ono et al. teach the entire sequence of the HBV genome and define the boundaries of the HBV genes. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligos taught by Oh et al. inhibited HBV replication (see the abstract), to use the sequence

taught by Ono et al. to design other oligos that were complementary to portions of either the X or P gene for the purpose of inhibiting HBV replication.

15. Claims 1-4, 15-35, 37-39, 44, 50, and 51 are rejected under 35 U.S.C. § 103 as being unpatentable over Offensberger et al. (IDS, B6) in view of Ono et al. (Nucleic Acids Res., 1983, 11(6): 1747-1757).

The claims are drawn to an oligonucleotide complementary to a portion of the HBV RNA having a nucleotide sequence selected from the group consisting of SEQ ID NOs 1-31 and 42-48 (Claim 1), more narrowly recited in Claims 2-4 as an oligonucleotide having SEQ ID NOs 1-3, respectively, or in Claims 15-35 and 37-39 as having SEQ ID NOs 14-44 or 46-48, respectively. These oligos are described in Table 1 and Figure 1 as being complementary to the preC region, and the core protein-encoding region, respectively. Claim 44 requires that the oligo of Claim 1 have at least one deoxynucleotide. Claims 50 and 51 are drawn to a pharmaceutical composition comprising at least one or two oligonucleotides, respectively.

Applicants state in the specification, page 4, lines 15-20, that the oligonucleotides designed by Offensberger et al. were directed to the 5' region of the pre-S gene and were shown to inhibit replication of duck HBV *in vivo*. This is supported in the abstract of the reference. However, other oligos were also

tested by Offensberger et al. as depicted in Figure 1 and described on page 1257, column 2, lines 24-30. One oligonucleotide, AS 5, was directed to the start of the polymerase region and four oligonucleotides, AS 6-9, were directed to the preC/C region. All oligonucleotides led to a decrease of intracellular viral intermediates, although AS 2 (directed to the preS region) and 6 (directed to the preC region) were described as the most effective (page 1257, column 2, lines 38-49). In addition, it is well known in the art, as depicted in both Figure 1 of the reference and Figure 1 of the instant specification, that the genes of HBV overlap eachother on the genome. Thus, an oligo directed toward the start of the P region that is effective at inhibiting HBV replication would also suggest that an oligo directed toward the C region would also be effective since the P region begins within the C region.

Offensberger teach oligos that are complementary to duck HBV and do not teach oligos that are complementary to human HBV. However, Ono et al. teach the entire sequence of the HBV genome and define the boundaries of the HBV genes. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligos taught by Offensberger et al. inhibited HBV replication in ducks, to target the regions taught by Offensberger et al. by designing oligos that are complementary to the equivalent regions of human HBV for the purpose of inhibiting HBV replication in humans.

16. Claims 1-9, 14-18, 33-35 and 37-44 are rejected under 35 U.S.C. § 103 as being unpatentable over Zhenghong et al. (Virologica Sinica, March 1995, 10(1): 34-40) in view of Ono et al. (Nucleic Acids Res., 1983, 11(6): 1747-1757).

The claims are drawn to an oligonucleotide complementary to a portion of the HBV RNA having a nucleotide sequence selected from the group consisting of SEQ ID NOs 1-31 and 42-48 (Claim 1), more narrowly recited in Claims 2-9 as an oligonucleotide having SEQ ID NOs 1-8, respectively, or in Claims 14-18 as having SEQ ID NOs 13-17, respectively, or in Claims 33-35 and 37-39 as having SEQ ID NOs 42-44 and 46-48, respectively. The other rejected claims are described above.

Zhenghong et al. teach antisense oligodeoxynucleotide phosphorothioates directed against the upstream region of the core gene initiation codon (#1893-1907), against the region upstream of the polymerase coding gene initiation region (#2297-2313), and against the 3' region of 3.5 kb RNA for initiation of reverse transcription (#1817-1831) (see the abstract). Although these are not the exact boundaries of the targeted positions described by the Applicants for the instant oligos of the rejected claims, the oligos of Zhenghong et al. overlap those encompassed by the above claims.

Ono et al. teach the entire sequence of the HBV genome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the

oligos taught by Zhenghong et al. inhibited HBV replication (as stated in the abstract), to use the sequence taught by Ono et al. to design other oligonucleotides that were complementary to the regions taught by Zhenghong et al. for the purpose of inhibiting HBV replication.

17. Claims 1-40, 44, 45, 48 and 49 are rejected under 35 U.S.C. § 103 as being unpatentable over Bresser et al. (U.S. Patent No. 5,225,326) in view of Ono et al. (Nucleic Acids Res., 1983, 11(6): 1747-1757).

The claims are drawn to an oligonucleotide complementary to a portion of the HBV RNA having a nucleotide sequence selected from the group consisting of SEQ ID NOs 1-31 and 42-48 (Claim 1), more narrowly recited in Claims 2-39 individually. The other claims are described above.

Bresser et al. teaches an in situ hybridization assay which is useful for detection of specific DNA or RNA species within a cell. The oligos are designed for a specific target molecule based on a known sequence (column 16, line 26) and can be RNA or DNA (column 16, line 14). Multiple probes each modified with a unique label may be used simultaneously (Column 14, lines 59-63). Bresser et al. also teaches that the probes may be provided in the form of a kit (column 15, lines 32-35). Although Bresser teaches in situ hybridization using probes complementary to HIV,

EBV and CMV (column 16, lines 44-46), Bresser et al. does not teach in situ hybridization with probes complementary to HBV.

Ono et al. teach the entire sequence of the HBV genome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the sequence taught by Ono et al. to design oligonucleotide probes for the detection and diagnosis of HBV using the in situ hybridization assay taught by Bresser et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bonnie Weiss whose telephone number is (703) 305-6775. The Examiner is available Monday through Thursday and every other Friday, from 8:00 to 5:30. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bonnie D. Weiss, Ph.D.

May 23, 1996

MINDY FLEISHER
SUPERVISORY PATENT EXAMINER
GROUP 1800